## REMARKS

***Status of the Claims***

Claims 1-3, 5-6, and 12-19 are currently pending in the present application. Claims 4 and 7-11 were previously canceled. Claims 1, 3, 5, 12, 15, 17, 18, and 19 are amended. Independent claims 1, 5, and 12 are amended to specify that the non-human mammal is selected from bovine, horse, pig, goat, rabbit, dog, cat, mouse, rat, hamster, or guinea pig and that the transgenic non-human mammals (claim 1), parts of the non-human transgenic mammals (claim 5) or cells from the transgenic non-human mammals comprise a transferred recombinant mouse or human GANP gene encoding and expressing a protein of SEQ ID NO: 2 or 4 or progeny thereof encoding and expressing said protein. Support for these elements is found throughout the application as originally filed, including, *e.g.*, page 9, lines 27-29, page 5-6, bridging paragraph, and page 10, lines 6-8. Claim 3 is also amended to cancel the dependency to claim 2. Claim 15 is amended to correct a typographical error. Claims 17-19 are amended to clarify that the GANP gene is operably linked to a human IgG enhancer. Claim 18 is further amended to correct a typographical error. The amendments are made without prejudice or disclaimer. No new matter is entered by way of these amendments. Applicants respectfully request reconsideration in view of the amendments and the remarks herein.

***Claim Objections***

Claim 15 is objected to for a typographical error. Specifically, the word "dose" in claim 15 is misspelled. Claim 15 is amended to correct the minor error. Accordingly, Applicants respectfully request withdrawal of the objection.

***Issues Under 35 U.S.C. § 112, First Paragraph, Enablement***

*Enablement*

Claims 1-3, 5, 6, 12, and 13-19 remain rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the enablement requirement. Specifically, the Examiner asserts that a skilled artisan would not have been able to express mouse or human GANP protein in the

wide variety of non-human animals, *e.g.*, generated by the allegedly wide variety of ES cells, as encompassed by the instant claims without undue experimentation, *see* Office Action, pages 5-6. The Examiner further alleges that a skilled artisan cannot reasonably predict from the present application that the claimed transgenic non-human mammals produce high affinity antibodies, *see* Office Action, page 6. The Examiner further asserts that the present application does not provide a correlation between mutation sites and the production of high affinity antibodies, *see* Office Action, page 6.

Although Applicants do not agree that the application fails to enable a skilled artisan to express mouse or human GANP protein in the non-human animals encompassed by the instant claims, the claims are amended to expedite prosecution. Specifically, independent claims 1, 5, and 12 are amended to specify that the transgenic non-human mammals, parts thereof or cells thereof are selected from the group consisting of bovine, horse, pig, goat, rabbit, dog, cat, mouse, rat, hamster, and guinea pig. Applicants submit that a skilled artisan using the guidance in the present application regarding the expression of GANP in mice, as described, *e.g.*, in Example 1 of the application as originally filed, coupled with the knowledge generally available to one of skill in the art regarding the generation of transgenic mammals, is sufficient to allow a skilled artisan to practice the claimed invention without undue experimentation. Accordingly, Applicants believe that this aspect of the enablement rejection is overcome.

Applicants further submit that the present application provides guidance enabling a skilled artisan to recognize that the described transgenic animals produce high affinity antibodies. As is understood by a skilled artisan, increased somatic hypermutations in transgenic animals are associated with affinity maturation of hapten specific B cells and enhanced antibody affinity, *see e.g.*, page 35, lines 1-2 and page 14, lines 28-29 in the originally filed application. As is evident from, *e.g.*, Figure 10 and page 34, lines 28-31, in the present application, GANP expression resulted in an increase in somatic hypermutations in the transgenic mice encompassed by the present claims in comparison to wild-type mice. Applicants respectfully submit that the claims do not describe specific mutations and, accordingly, the Examiner's argument is outside the scope of the instant claims.

In addition, Figure 29 demonstrates that high-affinity antibodies are generated using GANP transgenic mouse-derived hybridoma clones. The affinity of antibodies, generated after immunization with NP-CG antigen, *i.e.*, anti-NP antibody, was evaluated based upon the ability of the antibodies to bind to NP2-BSA, *i.e.*, two NPs coupled to BSA per molecule and NP17-BSA, *i.e.*, seventeen NPs coupled to BSA per molecule. Specifically, in ELISA analysis, the higher the value of NP2/NP17, (*i.e.*, the ability to bind to NP2-BSA/the ability to bind to NP17-BSA), the stronger the strength of binding to NP2-BSA, and, accordingly, the higher the affinity to the NP group. The results in Figure 29 show that the GANP transgenic mouse-derived hybridoma clones have higher affinity to the antigen compared to wild-type mouse-derived hybridoma clones. Accordingly, in contrast to the Examiner's assertions, a skilled artisan would have understood from the present application that the claimed transgenic mammals, parts thereof and cells thereof produce high affinity antibodies. In addition, a skilled artisan would have understood how to make and use such transgenic mammals, parts thereof and cells thereof.

Based upon the foregoing, Applicants submit that the present application enables the claims. Accordingly, Applicants respectfully request withdrawal of the rejection under 35 U.S.C. § 112, first paragraph, for enablement.

**Issues Under 35 U.S.C. § 112, Second Paragraph**

Claims 17-19 are rejected under 35 U.S.C. § 112, second paragraph as allegedly indefinite, see Office Action, page 7. Specifically, the Examiner asserts that the phrase "operably limited to a human IgG enhancer" is unclear.

Claims 17-19 are amended to specify "operably linked to a human IgG enhancer." Accordingly the rejection is overcome and Applicants respectfully request withdrawal of the rejection.

***Issues Under 35 U.S.C. § 103(a)***

Claims 1-5 remain rejected under 35 U.S.C. § 103(a) as allegedly obvious over Kuwahara *et al.*, *Blood*, 95:2321-2328, 2000, ("Kuwahara"), in view of Jaenisch, *Science*, 240:1468-1474, 1988, ("Jaenisch"), and further in view of Maas *et al.*, *J. Immunol.*, 162:6526-6533, 1999,

("Maas"), *see* Office Action, page 8. Claims 1 and 17-19 are also rejected under 35 U.S.C. § 103(a) as allegedly obvious over Kuwahara, in view of Jaenisch, and Maas, and further in view of Henderson *et al.* 1998, *Ann.Rev.Immunol.* 16:163-200, ("Henderson"), *see* Office Action, page 11. For the reasons set forth below, Applicants respectfully traverse the rejection.

The burden is on the Examiner to make a *prima facie* case of obviousness, which requires an objective analysis as set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966). In *KSR International v. Teleflex Inc.*, 550 U.S.__, 82 USPQ2d 1385 (2007), the Court affirmed that this analysis includes the following factual inquires: (1) determining the scope and content of the prior art; (2) ascertaining the differences between the claimed invention and the prior art; and (3) resolving the level of ordinary skill in the pertinent art. The Examination Guidelines for Determining Obviousness Under 35 U.S.C. § 103 in view of the Supreme Court Decision in *KSR International Co. v. Teleflex Inc.* state that, having undertaken the factual inquires of *Graham*, a rejection under 35 U.S.C. § 103 may be supported by one or more of the following rationales: (1) combining prior art elements according to known methods to yield predictable results; (2) simple substitution of one known element for another to obtain predictable results; (3) use of a known technique to improve similar devices in the same way; (4) applying a known technique to a known device ready for improvement to yield predictable results; choosing from a finite number of identified, predictable solutions, with a reasonable expectation of success; (5) variations that would have been predictable to one of ordinary skill the art; and (6) some teaching, suggestion, or motivation in the prior art that would have led one of ordinary skill to modify the prior art reference or to combine the prior art reference teachings to arrive at the claimed invention. 72 Fed. Reg. 57526, at 57529 (October 10, 2007). Each of the above-noted rationales requires predictability in the art and/or a reasonable expectation of success, and the Examiner must consider objective evidence, which rebuts such predictability and reasonable expectation of success. This objective evidence or secondary considerations may include unexpected results and/or failure of others (*e.g.*, evidence teaching away from the currently claimed invention), evidence of commercial success, and long-felt but unsolved needs, as found in the specification as-filed or other source. *Id.* When considering obviousness of a combination of known elements, the operative question is "whether the improvement is more

than the predictable use of prior art elements according to their established functions." *KSR* at_, 82 USPQ2d at 1396.

Independent claim 1 is directed to a transgenic non-human mammal selected from the group consisting of bovine, horse, pig, goat, rabbit, dog, cat, mouse, rat, hamster, and guinea pig, comprising a transferred recombinant mouse GANP gene or human GANP gene encoding and expressing a protein of SEQ ID NO: 2 or 4 or progeny thereof encoding and expressing said protein.

Independent claim 5 is directed to a part of a transgenic non-human mammal selected from the group consisting of bovine, horse, pig, goat, rabbit, dog, cat, mouse, rat, hamster, and guinea pig, comprising a transferred recombinant mouse GANP gene or human GANP gene encoding and expressing a protein of SEQ ID NO: 2 or 4, or progeny thereof encoding and expressing said protein.

Kuwahara discloses properties of the GANP gene. Jaenisch and Maas *et al.* each teach the use of heterologous promoters for tissue specific expression, and, in particular, B-cell specific expression. Henderson describes Ig expression in B-cells.

In contrast to the instant claims, Kuwahara fails to teach or suggest the regulation of GANP gene at a molecular level. Kuwahara, further, does not teach or provide guidance of how the GANP gene would function in an *in vivo* system, and in particular in a transgenic mammal. Specifically, Kuwahara fails to teach or suggest a transgenic non-human mammal or part thereof comprising a transferred recombinant mouse GANP gene or human GANP gene encoding and expressing a protein of SEQ ID NO: 2 or 4 or progeny thereof, encoding and expressing said protein. Jaenisch and Maas, which teach the use of heterologous promoters for tissue specific expression, and Henderson, which describes Ig expression in B-cells, fail to remedy the deficiencies of Kuwahara. Accordingly, none of the references, either alone or in combination, teach or suggest all of the elements of the instant claims.

In addition, Applicants respectfully submit that the transgenic animals described in the instant claims produce high affinity antibodies, which were previously unattainable by conventional methods, *see* page 7, lines 30-32 in the application as originally filed. A skilled artisan could not have reasonably predicted from the documents cited by the Examiner that

expressing GANP in non-human mammals would have resulted in this beneficial phenotype. Accordingly, Applicants submit that the instant claims are not obvious in view of the cited references. Based upon the foregoing, Applicants respectfully request that the rejection under 35 U.S.C. § 103(a) be reconsidered and withdrawn.

## CONCLUSION

In view of the above Amendment, Applicant believes the pending application is in condition for allowance.

Should there be any outstanding matters that need to be resolved in the present application, the Examiner is respectfully requested to contact Linda T. Parker, Reg. No. 46,046, at the telephone number of the undersigned below, to conduct an interview in an effort to expedite prosecution in connection with the present application.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37.C.F.R. §§1.16 or 1.17; particularly, extension of time fees.

Dated: DEC 29 2008

Respectfully submitted,

By _____
Gerald M. Murphy, Jr.
Registration No.: 28,977
BIRCH, STEWART, KOLASCH & BIRCH, LLP
8110 Gatehouse Road
Suite 100 East
P.O. Box 747
Falls Church, Virginia 22040-0747
(703) 205-8000
Attorney for Applicant